REMARKS

I. Pending Claims

Claims 1, 11, 12 and 29-45 are currently pending. Claims 11 and 39 have been amended, and claims 1, 12, 29, 30, 33, 35, 44 and 45 have been withdrawn from consideration. Applicants expressly do not disclaim the subject matter of any invention disclosed herein which is not set forth in the instantly filed claims. Applicants reserve the right to prosecute the non-elected claims in subsequent divisional applications.

II. Support for the Amendments

Claim 11 has been amended to incorporate the limitations of non-elected claim 1, from which it had depended. Claim 11 has also been amended to recite that in part a), the antibody specifically binds to an epitope of a polypeptide of SEQ ID NO:1, and in part b), the antibody specifically binds to an epitope of a polypeptide at least 90% identical to SEQ ID NO:1. Support for these amendments may be found in the Specification at page 7, lines 13-19. Claim 11 has been amended to replace the phrase "biologically active" with the phrase "enzymatically active." Support for this amendment may be found in the Specification at page 13, lines 1-14, wherein it is set forth that the polypeptide encoded by the amino acid sequence SEQ ID NO:1 is an enzyme called PROPHO. By these amendments, Applicants expressly do not disclaim equivalents of the invention which could include antibodies which bind to epitopes other than those recited in the claims. Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. While not conceding to the Patent Office position, it is believed that the claims, as amended, recite patentable subject matter.

Claim 39 has been amended to correct an inadvertent error in grammar. The phrase "isolating from the culture monoclonal antibody" has been corrected to state "isolating from the culture a monoclonal antibody."

No new matter is added by any of these amendments.

III. Restriction requirement/election

Election, with traverse, of the claims of Group II (encompassing claims 11, 31, 32, 34, and 36-43), drawn to an isolated antibody that binds to a polypeptide, a composition thereof, a method of preparing a polyclonal antibody, a polyclonal antibody, a composition thereof, a method of making a monoclonal antibody, a monoclonal antibody, and a composition thereof, is acknowledged.

Applicants acknowledge the Examiner's recognition that if the claims of Group II are found to be allowable, then the claims of Groups V-VII will be evaluated to determine if they are directed to processes of using the patentable product, and if so will be rejoined pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86; see also MPEP 821.04, *In re Ochiai*, and *In re Brouwer*).

IV. Declaration

The Examiner has indicated that the declaration is defective because the citizenship of Olga Bandman was not listed. Applicants are currently obtaining a newly executed copy of the declaration, which designates the citizenship of Olga Bandman. The declaration will be submitted to the USPTO upon receipt.

V. Specification/Informalities

In response to the Examiner's request that Applicants replace the title with one which is clearly indicative of the invention to which the claims are directed, the title has been amended to read "Protein Phosphatase Antibodies".

VI. Claim Objections

The Examiner has objected to Claims 11, 31, 32, 34, and 36-43 as being dependent upon a non-elected claim. Applicants have amended claim 11 to incorporate all limitations of claim 1, as suggested by the Examiner.

The Examiner has also objected to claim 39 as containing a grammatically incorrect term ("isolating from the culture monoclonal antibody"). Claim 39 has been amended to correct that

inadvertent error. The phrase has been corrected to state "isolating from the culture a monoclonal antibody."

Withdrawal of these objections is therefore respectfully requested.

VII. Indefiniteness rejection under 35 U.S.C. § 112, second paragraph

Claims 11, 31, 32, 34, and 36-43 have been rejected under 35 U.S.C. § 112, second paragraph, for allegedly being indefinite in the recitation of "biologically active." This rejection is respectfully traversed.

To expedite prosecution, claim 11 has been amended such that the term "biologically active" has been replaced with the term "enzymatically active." By this amendment, Applicants expressly do not disclaim equivalents of the invention which could include biologically active fragments of SEQ ID NO:1, which have activities other than enzymatic activity. Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application.

In view of the foregoing, the rejection under 35 U.S.C. § 112, second paragraph, has been overcome, and withdrawal is respectfully requested.

VIII. Written description rejection under 35 U.S.C. § 112, first paragraph

Claims 11, 31, 32, 34, 42, and 43 stand rejected under the first paragraph of 35 U.S.C. § 112, first paragraph, as being based on a specification which allegedly fails to reasonably convey to one of skill in the art that the Applicants had possession of the claimed invention at the time the application was filed. This rejection is respectfully traversed.

The Examiner states that claim 11 "is rejected because the genus of polypeptides to which the claimed genus of antibodies binds has not been fully described in the specification." The Examiner further states that "...the specification does not contain any disclosure of the structure all *[sic]* polypeptide sequences *comprising* SEQ ID NO:1 or *comprising* a naturally-occurring sequence that is at least 90% identical to SEQ ID NO:1 " (Office Action, February 7, 2003; page 5; emphasis in original). In addition, the Examiner states that "[r]egarding part b) of claim 11, the specification does not contain any disclosure of the function of all the naturally-occurring

polypeptide sequences that are at least 90% identical to SEQ ID NO:1 within the scope of the claimed genus" (Office Action, February 7, 2003; page 5).

The requirements necessary to fulfill the written description requirement of 35 U.S.C. 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed. Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) (emphasis added)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1," published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. [footnotes omitted]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The specification provides an adequate written description of the structure of the genus of polypeptides to which the claimed genus of antibodies binds

The subject matter encompassed by claims 11, 31, 32, 34, 42 and 43 is either disclosed by the specification or is conventional or well known to one skilled in the art.

First note that the language of independent claim 11 recites polypeptides "comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of . . . SEQ ID NO:1" (i.e., "variants" of SEQ ID NO:1). The polypeptide sequence of SEQ ID NO:1 is specifically disclosed in the application (see, for example, page 13, lines 12-30). Variants, and in particular, naturally occurring variants at least 90% identical to SEQ ID NO:1, are described at page 14, lines 1-5. Incyte clones in which the nucleic acids encoding the human PROPHO were first identified and libraries from which those clones were isolated are described, for example, at page 13, lines 6-11 of the Specification. Chemical and structural features of PROPHO are described, for example, on page 13, lines 12-26.

One of ordinary skill in the art would recognize polypeptide sequences which are naturally occurring variants that are at least 90% identical to SEQ ID NO:1. Given any particular naturally occurring polypeptide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:1. It would also be routine to determine whether such a variant had phosphatase activity, using the disclosed phosphatase assay (Specification at page 51, lines 15-22). Accordingly, the specification provides an adequate written description of the structure of the genus of polypeptides to which the claimed genus of antibodies binds.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA and antibodies which specifically bind to the proteins) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional

characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. §112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define antibodies which specifically bind to polypeptides in terms of chemical structure, rather than merely functional characteristics. For example, the language of independent claim 11, as amended, recites chemical structure to define the claimed genus:

11. (Once amended) An isolated antibody which specifically binds to an isolated polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1, wherein said antibody specifically binds to an epitope of a polypeptide of SEQ ID NO:1,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein said antibody specifically binds to an epitope of a polypeptide at least 90% identical to SEQ ID NO:1,

c) a fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the fragment has phosphatase activity, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1.

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. In the present case, there is no reliance merely on a description of functional characteristics of the antibodies which specifically bind to the polypeptides recited by the claims. The antibodies which specifically bind to the polypeptides defined in the claims of the present application recite structural features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base its written description inquiry "on whatever is now claimed," the Office Action failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA (1998) 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at

least 150 residues. (Brenner et al., pages 6073 and 6076.) Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins. (Brenner et al., page 6076.)

The present application is directed, *inter alia*, to antibodies that bind to naturally occurring PROPHO proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as PROPHO proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites, for example, antibodies which specifically bind to the polypeptides encoding "a naturally occurring amino acid sequence having at least 90% sequence identity to the sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 479 amino acid residues). This variation is far less than that of all potential PROPHO proteins related to SEQ ID NO:1, i.e., those PROPHO proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. §112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those case was based on the state of the art at essentially at the "dark ages" of recombinant DNA technology.

The present application has a priority date of June 11, 1997. Much has happened in the development of recombinant DNA technology in the 20 years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1, and the additional extensive detail provided by the

subject application, the present inventors were in possession of the claimed polynucleotide variants at the time of filing of this application.

B. No description of the function of the polypeptides is required to satisfy the written description requirement for the claimed antibodies

In support of his assertion that, regarding part b) of claim 11, the claimed genus of antibodies has not been fully described in the specification, the Examiner has asserted that the specification does not contain any disclosure of the function of all of the naturally occurring polypeptide sequences that are at least 90% identical to SEQ ID NO:1. Applicants respectfully remind the Examiner that disclosure of functional characteristics is merely one of the factors which can be used as evidence that Applicants were in possession of the claimed invention at the time of filing. For at least the reasons set forth above in sections A(1) - A(3), Applicants have provided an adequate written description of the claimed antibodies which specifically bind to a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1. Accordingly, this rejection should be withdrawn.

C. Summary

The Office Action failed to base its written description inquiry "on whatever is now claimed." Consequently, the Office Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of antibodies which specifically bind to the polypeptides defined by the present claims is adequately described, as evidenced by Brenner et al. and consideration of the claims of the '740 patent involved in *Lilly*. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

IX. Enablement rejection under 35 U.S.C. §112, first paragraph

Claims 11, 31, 32, 34, 42, and 43 have been rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter of the invention in such a way as to enable one of skill in the art to make and/or use antibodies which specifically bind to the recited polypeptides. In particular, the Examiner has asserted that the specification "while being enabling for an antibody that specifically binds the amino acid sequence of SEQ ID NO:1, does not reasonable provide enablement for an antibody that specifically binds: *any* polypeptide *comprising* the polypeptide of SEQ ID NO:1 or *any* polypeptide comprising an amino acid sequence having at least 90% identity to SEQ ID NO:1" (Office Action, February 7, 2003, paragraph bridging pages 5 and 6; emphasis in original). The Examiner also states that "the disclosure is limited to an antibody that specifically binds the polypeptide of SEQ ID NO:1. There is no disclosure in the specification or the prior art as to other polypeptides that comprise the polypeptide of SEQ ID NO:1 or other polypeptides comprising an amino acid sequence that have *[sic]* 90% or more identity to SEQ ID NO:1" (Office Action, February 7, 2003; page 6, lines 21-25). Such, however, is not the case.

Clearly, one of ordinary skill would readily be able to recognize a sequence comprising the explicitly disclosed sequence of SEQ ID NO:1. In addition, variants of SEQ ID NO:1 are disclosed in the specification at, for example, page 3, lines 2-6; page 12, lines 21-28; and page 14, lines 1-5 and lines 12-22.

Further, note that the claims recite not only that the polypeptides have at least 90% sequence identity to SEQ ID NO:1, but also have **"a naturally occurring amino acid sequence"** (which, of course, also includes their equivalents).

Furthermore, the Specification discloses methods to make antibodies which specifically bind to a polypeptide having **any** particular amino acid sequence (e.g., Specification at page 28, line 5 to page 29, line 14; and page 51, line 25 to page 52, line 9). Given the information provided by SEQ ID NO:1 (the amino acid sequence of PROPHO), one of skill in the art would be able to routinely obtain antibodies which specifically bind to any of the recited variants of SEQ ID NO:1, including "a polypeptide comprising a *naturally occurring* amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." For example, an animal could be immunized with any of the recited variants of SEQ ID NO:1, antibodies could be isolated from the animal, and the antibodies could be screened to identify antibodies which specifically bind to the polypeptide.

Likewise, the specification discloses methods to use antibodies which specifically bind to a polypeptide having **any** particular amino acid sequence in, for example, the purification of such polypeptides (e.g., at page 52, lines 11-21), the detection and/or measurement of such polypeptides (e.g., at page 23, lines 11-18; and page 35, line 14 to page 36, line 2), and the competitive screening of drug candidates (e.g., at page 42, lines 18-21). Given the information provided by SEQ ID NO:1 (the amino acid sequence of PROPHO), one of skill in the art would be able to routinely use antibodies which specifically bind to any of the recited variants of SEQ ID NO:1, including "a polypeptide comprising SEQ ID NO:1 " and "a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." For example, an antibody which specifically binds to any of the recited variants of SEQ ID NO:1 could be coupled to an activated chromatographic resin, and this resin could then be used in an immunoaffinity column to purify the polypeptide.

With respect to the Examiner's statement that "the specification fails to teach how to make and use an antibody that binds any polypeptide *comprising* the polypeptide of SEQ ID NO:1 as the claim, as written, does not require the antibody to specifically bind SEQ ID NO:1, but allows for an antibody to that is specific for amino acid sequence other than SEQ ID NO:1 that *comprises* the polypeptide" (Office Action, February 7, 2003; page 7, lines 11-15; emphasis in original), Applicants respond as follows.

To expedite prosecution, claim 11 has been amended such that it recites antibodies which bind to an epitope of SEQ ID NO:1, or which bind to an epitope of a polypeptide at least 90% identical to SEQ ID NO:1. By these amendments, Applicants expressly do not disclaim equivalents of the invention which could include antibodies which bind to epitopes other than those recited in the claims. Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. While not conceding to the Patent Office position, it is believed that the claims, as amended, recite patentable subject matter.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.

> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Office Action has failed to provide any **reasons** why one would doubt that the guidance provided by the present specification would enable one to make and use the claimed antibodies which specifically bind to the recited variants and fragments of SEQ ID NO:1. Hence, a *prima facie* case for non-enablement has not been established with respect to the claimed antibodies which specifically bind to the recited variants and fragments of SEQ ID NO:1.

For at least the above reasons, withdrawal of this rejection is requested.

CONCLUSION

The enablement, written description rejection, and indefiniteness rejections regarding the variant language should be withdrawn, based on at least the arguments presented above.

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact Applicants' Attorney at (650) 855-0555.

Please charge Deposit Account No. **09-0108** in the amount of **$ 110.00** as set forth in the enclosed fee transmittal letter. If the USPTO determines that an additional fee is necessary, please charge any required fee to Deposit Account No. **09-0108.**

Respectfully submitted,
INCYTE CORPORATION

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE TITLE

The title has been amended as follows: "[Human] Protein Phosphatase Antibodies."

IN THE CLAIMS

Claims 11 and 39 have been amended as follows:

11. (Once amended) An isolated antibody which specifically binds to [a polypeptide of claim 1] an isolated polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1, wherein said antibody specifically binds to an epitope of a polypeptide of SEQ ID NO:1,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, wherein said antibody specifically binds to an epitope of a polypeptide at least 90% identical to SEQ ID NO:1,

c) an enzymatically active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, and

d) an immunogenic fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1.

39. (Once amended) A method of making a monoclonal antibody with the specificity of the antibody of claim 11, the method comprising:

a) immunizing an animal with a polypeptide consisting of the amino acid sequence of SEQ ID NO:1, or an immunogenic fragment thereof, under conditions to elicit an antibody response,

b) isolating antibody producing cells from the animal,

c) fusing the antibody producing cells with immortalized cells to form monoclonal antibody-producing hybridoma cells,

d) culturing the hybridoma cells, and

e) isolating from the culture a monoclonal antibody which binds specifically to a polypeptide comprising the amino acid sequence of SEQ ID NO:1.